At page 35, line 22, please change "Figure 1" to --FIG. 1A-1C--.

At page 35, line 23, please change "Figure 1" to --FIG. 1A-1C--.

At page 35, line 24, please change "Figure 1" to --FIG. 1A-1C--.

At page 35, line 26, please change "Figure 1" to --FIG. 1A-1C--.

At page 35, line 27, please change "Figure 1" to --FIG. 1A-1C--.

At page 35, line 28, please change "Figure 1" to --FIG. 1A-1C--.

At page 49, lines 14-15, please change "FIG. 1" to --FIG. 1A-1C--.

At page 49, line 17, please change "FIG. 1" to --FIG. 1A-1C--.

At page 56, line 29, please change "FIG. 1" to --FIG. 1A-1C--.

At page 57, line 5, please change "FIG. 2" to --FIG. 2A-2B--.

At page 57, line 9, please change "FIG. 1" to --FIG. 1A-1C--.

At page 57, line 10, please change "FIG. 2" to --FIG. 2A-2B--.

At page 58, line 18, please change "FIG. 1" to --FIG. 1A-1C--.

At page 58, line 27, please change "FIG. 2" to --FIG. 2A-2B--.

At page 59, line 8, please change "FIG. 1" to --FIG. 1A-1C--.

At page 59, line 8, please change "FIG. 2" to --FIG. 2A-2B--.

At page 65, line 23, please change "Figure 2" to --FIG. 2A-2B--.

At page 65, line 24, please change "Figure 2" to --FIG. 2A-2B--.

Remarks

After entry of the foregoing amendments, claims 27-46 will be pending in the captioned application, with claims 27, 32, 37, and 43 being the independent claims.

I. The Amendments to the Specification

The amendments to the specification set out above are required to bring the specification into conformity with the formal drawings submitted herewith and to correct obvious typographical errors. Support for the amendments submitted herein are found throughout the specification and the originally filed figures. None of these amendments introduce new matter.

Applicants note that the amendment to page 7, line 14, of the specification presented herein is necessary to introduce text from informal Figure 3. Thus, support for the amendment of page 7, line 14, can be found in originally filed Figure 3. This amendment introduces no new matter.

II. The Rejection of the Claims under 35 U.S.C. § 101

The Examiner has rejected claims 27-46 of the captioned application under 35 U.S.C. § 101, on the basis that "they are drawn to an invention with no apparent or disclosed specific and substantial credible utility." (Paper No. 5, page 2.) In particular, the Examiner asserts that, "[t]he instant application does not disclose the biological role of . . . [the described] protein or its significance." (Paper No. 5, page 2.) As explained below, Applicants respectfully disagree.

The Examiner's rejection severely conflicts with the U.S. Patent & Trademark Office's own "Revised Interim Utility Guidelines Training Materials" (Utility Guidelines). According to the Utility Guidelines, "[t]he examiner should determine whether any asserted utility is specific and substantial, and if so, determine whether such asserted utility is credible." (Utility Guidelines, page 3.) The Utility Guidelines provide the following discussion of what is considered to be a "specific utility":

> A utility that is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention. For example, a claim to a

> polynucleotide whose use is disclosed simply as a "gene probe" or a "chromosome marker" would not be considered to be *specific* in the absence of a disclosure of a specific DNA target. . . .

(Utility Guidelines, page 5.)

Applicants point out in the captioned application that DR3-receptor polypeptides have specific utilities. For example, the captioned application indicates that DR3-receptor polypeptides induce apoptosis.[1] (Specification, *inter alia*, page 38, lines 5-13; and page 39, lines 3-6.) The accuracy of this statement is confirmed by the data provided in Example 6 of the captioned application which, as the Examiner clearly recognizes, teaches that "overexpression of DR3 in a heterologous host[2] leads to cell death . . . ." (Paper No. 5, page 3.) Thus, DR3-receptor polypeptides have a specific utility (*e.g.*, inducing apoptosis) which distinguishes them from polypeptides in general. Applicants assert that no more is needed to satisfy the "specific utility" prong of the utility analysis set forth in the Utility Guidelines.

Regarding the "substantial utility" prong of the utility analysis set forth in the Utility Guidelines, as noted above and conceded by the Examiner, DR3-receptor polypeptides induce apoptosis. One skilled in the art would thus clearly recognize that DR3-receptor polypeptides have real world use. (*See In re Brana*, 34 U.S.P.Q.2d 1437, 1442 (Fed. Cir. 1995) (citations omitted) (noting that demonstration that a compound has a pharmacological activity satisfies the utility requirement); MANUAL OF PATENT EXAMINING PROCEDURES, Seventh Edition, Rev. 1 § 2107.02 III (February 2000) (stating "[i]f reasonably correlated to the particular therapeutic or

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[1]While the claims of the captioned application are directed to nucleic acids, Applicants have chosen to discuss herein utilities related to the polypeptide expression products of these nucleic acids but reserve the right to assert in the future that nucleic acids of the invention have practical utility regardless of whether they encode DR3-receptor polypeptides.

[2]Applicants note that the cells used in Example 6 are of human origin. Thus, these cells are heterologous only in the sense that nucleic acid encoding the DR3-receptor polypeptide has been inserted into them.

pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process. . . .) (citations omitted).)

Applicants further note that utilities asserted in the captioned application for DR3-receptor polypeptides are also credible. The Utility Guidelines provide that "*[a]n assertion is credible unless* (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. . . ." (Utility Guidelines, page 5 (emphasis added).) The Examiner has provided no evidence that (1) the logic underlying Applicants' assertions of utility is seriously flawed or (2) the facts upon which Applicants base the assertions of utility are inconsistent with the logic underlying the assertions.

Applicants note that the Examiner appears to base his assertion that the utility requirement has not been satisfied for claims 27-46 in part on the position that "Applicant's discovery that over expression of DR3 in a heterologous host leads to cell death does not provide one of ordinary skill with a specific substantial utility, since this appears to be an inherent property of all receptor proteins containing a death domain." (Paper No. 5, page 3.) Applicants are confused by the Examiner's statement. Applicants DR3-receptor polypeptides are clearly useful - they lead to cell death - the fact that certain other proteins may possess similar activity does not detract from the utility of DR3.

In support of Applicants' position, the Examiner's attention is drawn to Example 10 of the Utility Guidelines. (Utility Guidelines, pages 53-55.) In particular, the DNA fragment described in Example 10 encodes a polypeptide identified as a DNA ligase *solely* on the basis of homology with known ligases. Example 10 states that, under the particular circumstances, a rejection of the exemplified claim should not be made under 35 U.S.C. § 101. (Utility Guidelines, page 55.) Applicants point out that Example 10 does not indicate that the

exemplified claim should be rejected on the basis that ligation activity is an inherent property of all DNA ligases. Further, such an application of the utility requirement would render most nucleic acids and polypeptides unpatentable regardless of how well characterized these molecules were at the time of filing. Applicants do not believe that such a result is the intention of the Utility Guidelines or comports with the current state of the law.

In view of the comments set out above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 27-46 under 35 U.S.C. § 101.

III. The Rejection the Claims under 35 U.S.C. § 112, First Paragraph

A. Claims 27-46

The Examiner has rejected claims 27-46 of the captioned application under 35 U.S.C. § 112, first paragraph, "as failing to adequately teach how to use the instant invention for those reasons given above with regard to the rejection of these claims under 35 U.S.C. § 101." (Paper No. 5, page 4.) Applicants respectfully disagree and note that this rejection has been addressed above with regard to the rejection of these claims under 35 U.S.C. § 101.

Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 27-46 under 35 U.S.C. § 112, first paragraph.

B. Claims 43-46

The Examiner has rejected claims 43-46 under 35 U.S.C. § 112, first paragraph, on the basis that "the instant specification does not provide a written description or the guidance needed to make a polypeptide comprising other than all or a functionally specific portion of the amino acid sequence presented in either of SEQ ID NO:2 or 4 of the instant application." (Paper No.

5, page 4.) In particular, the Examiner asserts that, "a polypeptide which could be encoded by [the claimed nucleic acid] would bear little or no resemblance to any polypeptide which is disclosed in the instant application." (Paper No. 5, page 4.) The Examiner further asserts that:

> Even if [claim 43] were limited to an isolated polypeptide which is encoded by a polynucleotide which hybridized [sic] to the complement of a nucleic acid having nucleotides 1245 to 1457 of SEQ ID NO:1 under the specified hybridization conditions, the instant specification does not disclose how to make or use that polypeptide since the majority of polypeptides which could be made by the claimed method would not be expected to retain the structure or function of that single native protein described in the instant specification.

(Paper No. 5, pages 4-5.)

The Examiner then cites *In re Fisher*, 166 U.S.P.Q. 18 (CCPA 1970), and states that "[b]ecause the instant specification does not identify those amino acid residues in either of SEQ ID NO:2 or 4 which are essential for the biological activity and structural integrity of a human DR3 protein and those residues which are either expendable or substitutable an artisan could not produce DR3 proteins differing from SEQ ID NO:2 or 4 by even a single amino acid . . . ." (Paper No. 5, page 5.)

As explained below, Applicants respectfully disagree with the Examiner but have amended claim 43 to recite that proteins which fall within the scope of this claim bind an antibody having binding specificity for a polypeptide consisting of amino acids 350 to 420 of SEQ ID NO:2. Applicants have also added "complement" language to claim 43 to address the Examiner's concerns. Applicants reserve the right to pursue the subject matter of original claim 43, as well as the subject matter of associated dependent claims, in continuing applications.

Applicants assert that one skilled in the art could routinely make and use polypeptides that fall within the scope of claims 43-46 as amended herein. In particular, methods for producing polypeptides which have specific amino acid sequences are both known in the art and

disclosed in the captioned application. For example, polypeptides encoded by polynucleotides which hybridize to the complement of nucleotides 1245-1457 of SEQ ID NO:1 can be produced from polynucleotides having nucleotide sequences which differ from that shown in SEQ ID NO:1. Example of methods which can be used to prepare such polynucleotides include site-directed mutagenesis and alanine scanning mutagenesis. (*See* Specification, page 31, lines 8-12.)

Claim 43 defines polypeptides which fall within its scope on the basis of *structural* characteristics. More specifically, in order for polypeptides to fall within the scope of claim 43, these polypeptides must be encoded by polynucleotides which hybridize to another polynucleotide which consists of the complement of nucleotides 1245 to 1457 of SEQ ID NO:1. Thus, the structures of polypeptides which fall within the scope of amended claim 43 are determined by the structures of polynucleotides which encode these polypeptides

Further, Applicants have included a *functional* limitation in amended claim 43 directed to a DR3 receptor property disclosed in the specification (*i.e.*, antibody binding specificity). (*See, e.g.*, Specification, page 34, line 17, to page 36, line 11; page 36, line 24, to page 37, line 21; and Figure 4.) In particular, proteins that fall within the scope of amended claim 43 must bind an antibody having binding specificity for a polypeptide consisting of amino acids 350 to 420 of SEQ ID NO:2. Applicants note that the specification provides both hybridization assays and methods for identifying polypeptides which have activity recited in claim 43. (*See, e.g.*, Specification, page 15, line 18, to page 16, line 15; page 36, line 24, to page 37, line 21; and Figure 4.)

In response to the Examiner's statement that "the instant specification does not identify those amino acid residues in either of SEQ ID NO:2 or 4 which are essential for the biological activity and structural integrity of a human DR3 protein and those residues which are expendable or substitutable an artisan could not produce DR3 proteins differing from SEQ ID NO:2 or 4 by

even a single amino acid . . . ." (Paper 5, page 5). Applicants point out that antigenic regions of the DR3 receptor are set out in Figure 4 of the captioned application. In particular, Applicants draw the Examiner's attention the Jameson-Wolf Antigenic Index portion of Figure 4. Further, one skilled in the art, using teachings provided in the captioned application, could readily generate and identify polypeptides which fall within the scope of amended claim 43.

Applicants thus assert that the captioned application enables one skilled in the art to practice the full scope of claims 43-46. This is so because one skilled in the art in possession of the disclosure of the captioned application could routinely identify, make and use polypeptides which are the subject matter of these claims.

In view of the above comments and the amendments to claims 43-46 submitted herein, Applicants respectfully request that the Examiner reconsider and withdraw the outstanding rejection of these claims under 35 U.S.C. § 112, first paragraph.

C. Claims 32-36

The Examiner has rejected claims 32-36 under 35 U.S.C. § 112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention." (Paper No. 5, page 6.)

The Examiner asserts that, "[claims 32-36] expressly require the biological material recited therein." (Paper No. 5, page 6.) The Examiner further asserts that Applicants, their assignee, or their agent must provide a declaration containing a number of statements. (Paper No. 5, pages 6-7.) In particular, the Examiner has, in essence, requested that Applicants provide a declaration which contains statements indicating that the requirements of 37 C.F.R. § 1.808(a) and M.P.E.P. § 2408 will be complied with for the cDNA clone contained in ATCC Deposit No. 97456. The Examiner has also requested that the declaration also contain statements that (1) the

"deposit has been made in a depository affording permanence of the deposit and ready accessibility thereto by the public if a patent is granted" and (2) "the deposited material has been accorded a specific, recited accession number." (Paper No. 5, page 6.)

A Declaration for Deposited Biological Materials signed by an attorney of record addressing these issues is submitted herewith.

The Examiner also asserts that, "the deposit must be referred to in the body of the specification and be identified by deposit (accession number) number, name and address of the depository and the complete taxonomic description." (Paper No. 5, page 7.)

Applicants note that the specification, at page 8, lines 1-5, reads, in relevant part, as follows:

> The nucleotide sequence shown in FIG. 1 [SEQ ID NO:1] was obtained by sequencing the HTTNB61 clone, which was deposited on March 1, 1996 at the American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209, USA, and given Accession Number 97456. The deposited clone is contained in the pBluescript SK(-) plasmid (Stratagene, LaJolla, CA).[3]

In view of the above, Applicants point out that the specification of the captioned application contains the information referred to above by the Examiner.

In view of the submission herewith of the Declaration for Deposited Biological Materials and the above remarks, it is respectfully submitted that the Examiner's positions regarding the biological deposit are moot. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 32-36 under 35 U.S.C. § 112, first paragraph.

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[3]The text of the captioned application set out here was amended by the Preliminary Amendment filed June 16, 1999 to refer to the new address of the American Type Culture Collection. These amendments have been incorporated into the text shown here.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider the outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 202-789-5509.

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 19-0036.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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